REMARKS

I. Status of the Claims

Claims 1, 2 and 4-36 are pending, claims 18 and 19 having been withdrawn by the Examiner. Accordingly, claims 1, 2, 4-17 and 20-36 are pending and at issue.

Applicants thank the Examiner for the careful consideration of this application. Reconsideration of the present application is respectfully requested in view of the amendments above and the remarks below.

II. Rejections Under 35 U.S.C. § 103

A. Illum in view of Grebow

Claims 1-2, 4-9, 12, 14-17 and 20-36 stand rejected as obvious over U.S. Patent No. 6,387,917 issued to Illum et al. (hereafter "Illum"), in view of U.S. Patent No. 5,026,825 issued to Grebow et al. (hereafter "Grebow").

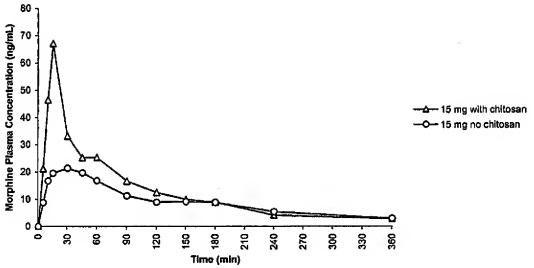
According to the Office Action:

> While Illum discloses the use of antimicrobial agents, Illum does not disclose the use of benzalkonium chloride, disodium EDTA, sodium benzoate, and combinations thereof.
>
> Grebow discloses an intranasal formulation comprising antimicrobial agents including benzalkonium chloride and disodium EDTA (Examples). They are present in the amount of 0.001-2.0% (w/v) (column 11, lines 55-63).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the specific antimicrobial agents of Grebow into the formulation of Illum since Grebow discloses [that] they are suitable for use in nasal inhalant formulation.

(Office Action at 5-6). Applicants respectfully disagree that the Office Action has established a *prima facie* case of obviousness and request reconsideration in view of the following remarks.

The claims of the present application related to medicaments that provide controlled release of morphine (i.e., a substantially linear uptake). Upon combining morphine with chitosan at specified molecular ratios, the resulting formulation provides substantially linear absorption of morphine upon being administered.

This is shown, for example, in Figure 1 of the present application, which is reproduced below.



Linear absorption provides a controlled increase in therapeutic plasma levels of morphine during the absorption or uptake phase after nasal administration. Such controlled absorption of morphine reduces the risk of overly rapid absorption and thus reduces the risk of overdose (see specification page 7, lines 8-18). Accordingly, the application addresses and overcomes a large obstacle in morphine therapy by reducing the risk of overdose.

In addition to providing a controlled release of morphine, the medicaments of the present claims are also stable. It is noted that Morphine is not readily soluble in all solvents. Furthermore, morphine is known to have several degradation products that, themselves, could present stability concerns. Degradation products may include psuedomorphine (2,2'-bimorphine) and phenanthrene derivatives. The independent claims of the present application recite an antimicrobial agent selected from benzalkonium chloride, disodium EDTA, or a combination thereof. These antimicrobial agents are believed to contribute the stability of the medicament.

A *prima facie* case of obviousness must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. *See* M.P.E.P. §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, rather than Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

At least because there would have been no reasonable expectation of successfully substituting the antimicrobial agents in Grebow's calcitonin formulation with the morphine formulations disclosed in Illum to provide a stable formulation, a *prima facie* case of obviousness has not been established. Grebow's formulations are limited to calcitonin, and analogs thereof. A person of ordinary skill in the art would have no expectation of successfully combining antimicrobial agents used in a calcitonin formulation (a polypeptide hormone), with morphine (a small molecule opiate analgesic known to present stability concerns) to provide a

stable formulation. In contrast, the medicaments of the present application are stable, and further provide a controlled release of morphine.

It is further noted that Grebow's formulations contain Δ-aminolveulinic acid, which inhibits the degradation of calcitonin. As noted above, morphine has decomposition products, such as phenanthrene derivatives, that themselves, may present stability problems. Illum formulations do not contain agents for the purpose of preventing degradation of morphine. Accordingly, one of ordinary skill in the art would have no reasonable expectation of successfully employing agents from Grebow, like antimicrobial agents, into Illum's formulations containing morphine and morphine degradation products which do not contain agents like Δ-aminolveulinic acid that prevent degradation of the active agent.

At least because one of ordinary skill in the art would have no expectation of incorporating agents from Grebow into the morphine formulations of Illum, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to claims 1-2, 4-9, 12, 14-17 and 20-36. Accordingly Applicants request that the obviousness rejection these claims be withdrawn.

B. Illum in view of Grebow, further in view of Tulin

Claim 11 stands rejected as obvious over Illum, in view of Grebow, and further in view of U.S. Patent No. 5,508,282 issued to Tulin-Silver et al (hereafter "Tulin"). Tulin is cited only for its teaching of ascorbic acid or sodium ascorbate. Tulin does not, however, overcome the deficiencies noted above with respect to Illum and Grebow. After consulting Tulin, there still would have been no reasonable expectation of successfully substituting the antimicrobial agents in Grebow's calcitonin formulation with the morphine formulations disclosed in Illum to provide a stable formulation.

In this regard, it is noted that Tulin's formulations contain caffeine and Vitamin C as active agents. Whereas morphine is a an opioid that is not readily soluble in all solvents, Vitamin C is readily soluble in water. It is not reasonable to expect success when substituting agents from a Vitamin C formulation into a morphine formulation, since it is more difficult to maintain stable morphine formulations.

At least because one of ordinary skill in the art would have no expectation of incorporating agents from Grebow into the morphine formulations of Illum, even after consulting Tulin, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to claim 11.

C. Illum in view of Grebow, further in view of Santus

Claim 13 stands rejected as obvious over Illum, in view of Grebow, and further in view of U.S. Patent No. 6,333,044 issued to Santus et al (hereafter "Santus"). Santus is cited only for its teaching of sodium benzoate. Santus does not, however, overcome the deficiencies noted above with respect to Illum and Grebow. After consulting Santus, there still would have been no reasonable expectation of successfully substituting the antimicrobial agents in Grebow's calcitonin formulation with the morphine formulations disclosed in Illum to provide a stable formulation. In this regard, it is noted that Santus relates to intranasal formulation containing Ketorolac®, as opposed to morphine, which is known to present stability concerns.

At least because one of ordinary skill in the art would have no expectation of incorporating agents from Grebow into the morphine formulations of Illum, even after consulting Santus, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to claim 13.

Conclusion

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections. Applicants further submit that the application is now in condition for allowance, and they earnestly solicit timely notice of the same. Should the Examiner have any questions, comments or suggestions in furtherance of the prosecution of this application, the Examiner is invited to contact the attorney of record.

Applicants submit herewith a Request for Continued Examination (RCE), a petition for a two-month extension of time and applicable fees. Should the Commissioner deem that any additional fees are due, the Commissioner is authorized to debit Baker Botts L.L.P. Deposit Account No. 02-4377, Order Number 077350.0235 for any additional fees that may be due in association with this filing.

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Respectfully submitted,

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